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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/416,920	04/21/95	MILTENYI S	212302000320

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EXAMINER	
SCHWADRON, R	
ART UNIT	**PAPER NUMBER**
1644	19

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trad marks

Office Action Summary

Application No.	Applicant(s)
08/416,920	Miltenyi et al.
Examiner	**Group Art Unit**
Ron Schwadron, Ph.D.	1644

☐ Responsive to communication(s) filed on _____.

☒ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-30, 34-51, 53-56, 69, and 70* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-30, 34-51, 53-56, 69, and 70* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

1. Claims 1-30,34-51,53-56,69,70 are under consideration. Claims 1,10,14,22,26-28,43,47 have been amended. Regarding claim 20, said claim was erroneously amended in the amendment filed 6/12/98 and still needs to be corrected (eg. it should be cancelled or amended to read on the subject matter of said claim as per the amendment filed 8/20/97).

RESPONSE TO APPLICANTS' ARGUMENTS

2. The non-statutory double patenting rejection, whether of the obvious-type or non-obvious-type, is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent. *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); *In re Van Ornam*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); and *In re Goodman*, 29 USPQ2d 2010 (Fed. Cir. 1993).
A timely filed terminal disclaimer in compliance with 37 CFR 1.321 (b) and (c) may be used to overcome an actual or provisional rejection based on a non-statutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.78 (d).
Effective January 1, 1994, a registered attorney or agent of record may sign a Terminal Disclaimer. A Terminal Disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

3. Claims 1-13,53-56,69,70 stand provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-6 of copending application Serial No. 08/441259 . Although the conflicting claims are not identical because the scope of claim 1 of 08/441259 differs from that of the instant invention in that it recites that the cells are not lysed as part of the procedure, both sets of claims read on methods that encompass positive selection of cells secreting a particular protein. Therefore, the two sets of claims under

consideration in this rejection would have been prima facie obvious in view of each other to one of ordinary skill in the art at the time the invention was made for the aforementioned reasons.

This is a *provisional* obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Applicant has indicated that a terminal disclaimer would be submitted at a later date if the instant application is found allowable.

4. Applicants need to update the status of all US patent applications (eg. first page of specification) disclosed in the specification (eg. now abandoned).

5. Claims 1-21,29,30,34-40,43-50,53-56,69,70 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the claimed method or kit which uses a high viscosity or gel forming medium such as gelatin or agarose or alginate, does not reasonably provide enablement for the claimed method or kit that does not use said ingredients. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims for the reasons elaborated in the previous Office Action. Applicants arguments have been considered and deemed not persuasive.

Manz et al. teach that, "In normal medium the secreted product will readily diffuse away and, in the approach described here, will label all cells covered with the affinity matrix, whether they are secreting or not."(page 1923, first column). Manz et al. later point out that a solution to this problem is to perform the assay in a high viscosity media (page 1923, first column). Thus, Manz et al. establish the need for high viscosity media to practice the instant invention. Therefore, the enablement is not commensurate with the scope of claims that do not recite the aforementioned ingredient as a component of the claimed method or kit.

Regarding applicants comments in the instant amendment, Manz et al. (an inventor of the instant application), discloses in a publication filed after the filing date of the instant invention, wherein said publication discloses the instant invention that, "In normal medium the secreted product will readily diffuse away and, in the approach described here, will label all cells covered with the affinity matrix, whether they are secreting or not."(page 1923, first column). Manz et al. later point out that a solution to this problem is to perform the assay in a high viscosity media (page 1923, first column). Thus, Manz et al. establish the need for high viscosity media to

practice the instant invention. Regarding Example 1 of the specification, said example actually discloses the need to use high viscosity media to actually distinguish secreting from nonsecreting cells (see page 28, last sentence, continued on next page). Example 1 in the specification indicates that depending on the parameters used, in the absence of high viscosity media it is not possible to distinguish secreting from nonsecreting cells (see page 27, last paragraph). Regarding the specification, page 18, Manz et al. teach that, "In normal medium the secreted product will readily diffuse away and, in the approach described here, will label all cells covered with the affinity matrix, whether they are secreting or not."(page 1923, first column). Manz et al. later point out that a solution to this problem is to perform the assay in a high viscosity media (page 1923, first column). Thus, Manz et al. establish the need for high viscosity media to practice the instant invention. Regarding the Assenmacher declaration filed 6/12/98, said declaration discloses that: "The requirement for embedding cells in media of high viscosity during the secretion period was overcome by optimizing incubation conditions with respect to cell density and incubation time."(page 3). Thus, the Assenmacher declaration filed 6/12/98 discloses that in order to obtain the results disclosed in said declaration it is necessary to optimize incubation conditions with respect to cell density and incubation time. However, the specification does not disclose such steps with regards to the claimed invention. Thus, the Assenmacher declaration filed 6/12/98 does not establish that the claimed invention is enabled in the absence of a high viscosity or gel forming medium such as gelatin or agarose or alginate because the Assenmacher declaration relies on a method which uses crucial steps wherein the crucial steps of the method are not disclosed in the specification.

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

7. Claims 14,15,29,30 stand rejected under 35 U.S.C. § 102(b) as being clearly anticipated by Kohler et al. for the reasons elaborated in the previous Office Action. Applicants arguments

have been considered and deemed not persuasive.

Regarding applicants comments, Kohler et al. teaches the methods of claims 14 and 15 (see page 469, section 2.8). Regarding applicants comments, Kohler et al. teach the method of claim 14, which is drawn to a method to label cells with a secreted product (see entire document), not a method to positively select cells. The cells are not lysed as part of the "labelling procedure" taught by Kohler et al.. The cells are not lysed until after the labelling procedure (eg. the cells are labelled with hapten, then in a separate step, the labelled cells are added to a source of complement, see section 2,8, page 469). Regarding applicants comments, claim 29 reads on progeny of cells which secrete a desired product (eg. hybridoma cells that secrete a desired antibody). The progeny of labelled cells produced by the claimed method will not be labelled because said cells are not the original labelled parent cells and the label or capture moiety would not be found on progeny cells. Therefore, the progeny of the cells of claim 29 are identical to hybridomas secreting a desired product (eg. any hybridoma cell). Kohler et al. teach hybridoma cells. Regarding cells separated by the claimed method, the labelled cells will not maintain the capture moiety/label for an indefinite period of time. All membrane bound molecules are eventually recycled and disappear from the cell surface after an appropriate length of time. After the capture moiety disappears from the cell surface, a hybridoma cell produced by the claimed method is identical any art hybridoma cell, such as those taught by Kohler et al. Regarding the process recited in claims 29 and 30, the method wherein the claimed product is made carries no patentable weight in said claims because the claimed product is identical to that of the prior art. The MPEP section 2113 (July 1998, page 2100-51) states:

Even though product-by process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." In re Thorpe, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985) (citations omitted) (Claim was directed to a novolac color developer. The process of making the developer was allowed. The difference between the inventive process and the prior art was the addition of metal oxide and carboxylic acid as separate ingredients instead of adding the more expensive pre-reacted metal carboxylate. The product-by-process claim was rejected because the end product, in both the prior art and the allowed process, ends up containing metal

carboxylate. The fact that the metal carboxylate is not directly added, but is instead produced in-situ does not change the end product.).

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. Claims 14-28,34-51 remain rejected under 35 U.S.C. § 103 as being unpatentable over Kohler et al in view of Hunt, Segal (US Patent 4,676,980) and prior art disclosed in the specification for the reasons elaborated in the previous Office Action. Applicants arguments have been considered and deemed not persuasive.

Regarding applicants comments in the instant amendment, Segal teaches bispecific antibodies (see Abstract). Segal teaches that bispecific antibodies can bind a cell surface antigen on the surface of a target cell and also bind another desired antigen, thus bringing the antigen to the cell surface (see columns 1 and 2). Thus, Segal teaches that bispecific antibodies can act as a bridge connecting two different antigens that are bound by the bispecific antibody. In view of such a teaching it would have been obvious to a routineer that TNP or any desired molecule that would have been used in the method taught by Kohler would have been connected to the surface via bispecific antibody. Regarding applicants comments about motivation to create the claimed invention, the M.P.E.P., section 2144 (July 1998), page 2100-115 teaches that with regards to the rationale/motivation supporting a rejection under 35 U.S.C. 103 that: "Rationale may be in a reference, or reasoned from common knowledge in the art, scientific principles, art-recognized equivalents, or legal precedent". In the instant rejection, the rationale has been reasoned from common knowledge in the art and scientific principles. Segal clearly teaches that bispecific antibodies can act as a bridge connecting two different antigens that are bound by the bispecific antibody. Regarding applicants comments about claims 14-21, Kohler et al. teaches the methods of claims 14 and 15 (see page 469, section 2.8). Kohler et al. teach the method of claim 14, which is drawn to a method to label cells with a secreted product (see entire document), not a method to positively select cells. The cells are not lysed as part of the "labelling procedure" taught

by Kohler et al.. The cells are not lysed until after the labelling procedure (eg. the cells are labelled with hapten, then in a separate step, the labelled cells are added to a source of complement, see section 2,8, page 469). Regarding applicants comments about the product of claims 22-28, it would have been obvious to a routineer that the product of claims 22-28 could have been used in the method of Kohler et al. , wherein labeling of the cell surface with any molecule for which negative selection of IgM producing antibodies was desired as per the method taught by Kohler for negative selection of antiTNP IgM antibodies. Regarding applicants comments in the instant amendment, the ingredients in the claimed kit would have been used in the method taught by Kohler et al. Segal teaches bispecific antibodies (see Abstract). None of the claims under consideration are drawn to methods of positive selection. The kits, cells and methods recited in the claims under consideration could be used in the method taught by Kohler et al.

10. Claim 69 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention for the reasons elaborated in the previous Office action. Applicants arguments have been considered and deemed not persuasive.

There is no support in the specification as originally filed for the methods of claims 69 and 70.

Regarding applicants comments about the specification, pages 25 and 26, there is no disclosure in said passages of the method of claim 69 wherein "bispecific antibodies and label moiety are added simultaneously to cells".

11. No claim is allowed.

12. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37

CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

13. Papers related to this application may be submitted to Group 1600 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Papers should be faxed to Group 1600 at (703) 305-3014.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dr. Ron Schwadron whose telephone number is (703) 308-4680. The examiner can normally be reached Monday through Thursday from 7:30 to 6:00. A message may be left on the examiners voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ms. Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Group 180 receptionist whose telephone number is (703) 308-0196.

RONALD B. SCHWADRON
PRIMARY EXAMINER
GROUP ~~1800~~ 1600

Ron Schwadron, Ph.D.
Primary Examiner
Art Unit 1644
July 15, 1999